

What is claimed is:

1. An expression cassette comprising a polynucleotide encoding a Ror polypeptide or homologues or derivatives or fragments or variants or mutants thereof
5 wherein said polynucleotide is under the control of a promoter operable in bone cells.
2. The expression cassette of Claim 1, wherein Ror polypeptide is Ror1 polypeptide.
- 10 3. The expression cassette of Claim 1, wherein Ror polypeptide is Ror2 polypeptide.
4. The expression cassette of Claim 1, wherein said promoter is heterologous to the coding sequence.
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5. The expression cassette of Claim 1, wherein the promoter is a bone-specific promoter.
6. The expression cassette of Claim 5, wherein the bone-specific promoter is a
20 rat 3.6 kb type I collagen or rat 1.7 kb osteocalcin promoter.
7. The expression cassette of Claim 1, wherein said promoter is an inducible promoter.
- 25 8. A vector comprising the expression cassette of Claim 1.
9. The vector of Claim 8, wherein the vector is a viral vector.
10. The vector of Claim 9, wherein said viral vector is selected from the group
30 consisting of a retroviral vector, an adenoviral vector, an adeno-associated viral vector, a vaccinia viral vector, and a herpes viral vector.
11. The expression cassette of Claim 1, wherein said expression cassette further comprises a polyadenylation signal.
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12. A host cell comprising an expression cassette comprising a polynucleotide encoding a Ror polypeptide or homologues or derivatives or fragments or variants or mutants thereof, wherein said polynucleotide is under the control of a promoter operable in eukaryotic cells, said promoter being heterologous to said polynucleotide.
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13. The host cell of Claim 12, wherein Ror polypeptide is Ror1 polypeptide.
14. The host cell of Claim 12, wherein Ror polypeptide is Ror2 polypeptide.
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15. A composition for modulating bone-related activity comprising an effective amount of Ror molecule or homologues or derivatives or fragments or variants or mutants thereof.
16. The composition of Claim 15, wherein Ror molecule is Ror1 molecule.
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17. The composition of Claim 15, wherein Ror molecule is Ror2 molecule.
18. The composition of Claim 15, further comprising a pharmaceutically acceptable carrier.
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19. The composition of Claim 15, wherein bone-related activity is osteoblast differentiation, osteoclast differentiation, osteoblast survival, osteoclast survival, osteoblast activity, or osteoclast activity.
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20. A method of screening for agents, the method comprising: (a) combining an agent with a Ror molecule; and (b) detecting an effect of said agent on Ror activity; wherein detection of a decrease or an increase in Ror activity is indicative of an agent being a bone-related agent.
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21. The method of Claim 20, wherein a decrease or an increase in Ror activity is detected by a decrease or an increase in Ror-induced inhibition of Wnt-3 signaling.
22. The method of Claims 20, wherein Ror molecule is Ror1 molecule and Ror activity is Ror1 activity.
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23. The method of Claims 20, wherein Ror molecule is Ror2 molecule and Ror activity is Ror2 activity.
24. The method of Claim 20, wherein Ror molecule is Ror2 molecule and a decrease or an increase in Ror activity is detected by a decrease or an increase in Ror2-induced activation of Wnt-1 signaling.
25. The method of Claim 20, wherein Ror molecule is a Ror polypeptide and a decrease or an increase in Ror activity is detected by a decrease or an increase in Ror autophosphorylation.
26. The method of Claim 25, wherein Ror polypeptide is Ror1 polypeptide, and Ror activity is Ror1 activity.
27. The method of Claim 25, wherein Ror polypeptide is Ror2 polypeptide, and Ror activity is Ror2 activity.
28. A method of screening for agents, the method comprising: (a) combining an agent with an isolated cell comprising a Ror promoter sequence operatively linked to a reporter gene; and (b) detecting an effect of said agent on reporter activity; wherein detection of a decrease or an increase in Ror promoter activity as measured by the reporter activity is indicative of an agent being a bone-related agent.
29. The method of Claim 28, wherein Ror promoter is Ror1 promoter.
30. The method of Claim 29, wherein Ror1 promoter is human Ror1 promoter.
31. The method of Claim 28, wherein Ror promoter is Ror2 promoter.
32. The method of Claim 31, wherein Ror2 promoter is mouse Ror2 promoter.
33. A method of screening for agents that modulate the binding of Ror polypeptide to a binding partner comprising: (a) contacting Ror polypeptide with a Ror binding partner in the presence of an agent; (b) contacting Ror polypeptide with a Ror binding partner in the presence of a control or in the absence of the agent; and

(c) selecting the agent that modulates Ror polypeptide binding to Ror binding partner by comparing the binding of said Ror polypeptide to the binding partner in step (a) to the binding of said Ror polypeptide to a binding partner in step (b).

5 34. The method of Claim 33, wherein Ror polypeptide is Ror2 polypeptide and Ror binding partner is Ror2 binding partner.

35. The method of Claim 34, wherein Ror2 binding partner is selected from the group consisting of ADP/ATP carrier protein, UDP-glucose ceramide
10 glucosyltransferase-like 1, 14-3-3 protein beta/alpha, 14-3-3 protein gamma, ribophorin I, arginine N-methyltransferase 1, cellular apoptosis susceptibility protein, NOTCH2 protein, and human skeletal muscle LIM-protein 3.

36. A method of modulating bone-related activity in a subject comprising
15 administering to a subject an agent which modulates target Ror molecule expression or activity.

37. The method of Claim 36, wherein said agent comprises one or more of Ror molecules or homologues or derivatives or fragments or variants or mutants thereof.
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38. The method of Claim 36, wherein said agent comprises one or more of Ror molecule binding partners or homologues or derivatives or fragments or variants or mutants thereof.

25 39. The method of Claims 36, wherein target Ror molecule is Ror1 molecule.

40. The method of Claims 36, wherein target Ror molecule is Ror2 molecule.

41. The method of Claim 36, wherein target Ror molecule activity is tyrosine
30 kinase activity.

42. The method of Claim 36, wherein bone-related activity is osteoblast differentiation, osteoclast differentiation, osteoblast survival, osteoclast survival, osteoblast activity, or osteoclast activity.
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43. The method of Claim 36, wherein said agent is selected from the group consisting of an antibody, a small molecule, a peptide, an oligopeptide, and a polypeptide.
- 5 44. The method of Claim 36, wherein said agent comprises an antisense nucleic acid or siRNA molecule specific for Ror gene and wherein antisense nucleic acid or siRNA molecule recognize and bind to a nucleic acid encoding one or more Ror polypeptides or homologues or derivatives or fragments or variants or mutants thereof.
- 10 45. The method of Claim 44, wherein Ror gene is Ror1 gene and Ror polypeptide is Ror1 polypeptide.
46. The method of Claim 44, wherein Ror gene is Ror2 gene and Ror polypeptide is Ror2 polypeptide.
- 15 47. The method of Claim 36, wherein said agent modulates expression and/or activity of target Ror molecules or homologues or derivatives or fragments or variants or mutants thereof by binding to Ror binding partners.
- 20 48. The method of Claim 47, wherein said agent inhibits expression and/or activity of target Ror molecules or homologues or derivatives or fragments or variants or mutants thereof by binding to Ror binding partners.
49. The method of Claim 47, wherein said agent enhances expression and/or activity of target Ror molecules or homologues or derivatives or fragments or variants or mutants by binding to Ror binding partners.
- 25 50. The method as in any one of Claims 47-49, wherein target Ror molecule is Ror2 molecule and Ror binding partner is Ror2 binding partner.
- 30 51. The method of Claim 50, wherein Ror2 binding partners are selected from the group consisting of ADP/ATP carrier protein, UDP-glucose ceramide glucosyltransferase-like 1, 14-3-3 protein beta/alpha, 14-3-3 protein gamma, ribophorin I, arginine N-methyltransferase 1, cellular apoptosis susceptibility protein, 35 NOTCH2 protein, and human skeletal muscle LIM-protein 3.

52. The method of Claim 36, wherein said agent modulates binding of Ror molecules or homologues or derivatives or fragments or variants or mutants thereof to Ror binding partners.

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53. The method of Claim 52, wherein said agent enhances binding of Ror molecules or homologues or derivatives or fragments or variants or mutants thereof to Ror binding partners.

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54. The method of Claim 52, wherein said agent inhibits binding of Ror molecules or homologues or derivatives or fragments or variants or mutants thereof to Ror binding partners.

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55. The method as in any one of claims 52, wherein Ror molecule is Ror2 molecule and Ror binding partner is Ror2 binding partner.

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56. The method of Claim 55, wherein Ror2 binding partners are selected from the group consisting of ADP/ATP carrier protein, UDP-glucose ceramide glucosyltransferase-like 1, 14-3-3 protein beta/alpha, 14-3-3 protein gamma, ribophorin I, arginine N-methyltransferase 1, cellular apoptosis susceptibility protein, NOTCH2 protein, and human skeletal muscle LIM-protein 3.

57. The method of Claim 36, wherein the agent is administered to isolated cells in culture.

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58. The method of Claim 57, wherein the cells are primary osteoblasts, immortalized cell lines of osteoblastic origin, or immortalized cell lines of non-osteoblastic origin.

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59. The method of Claim 58, wherein immortalized cell lines of osteoblastic origin are selected from the group consisting of HOB, U2OS, and SaOS-2 cells.

60. The method of Claim 36, wherein the agent is administered to a non-human transgenic animal.

61. The method of Claim 60, wherein, the transgenic animal is a mouse.

62. The method of Claim 60, wherein the agent is administered to a non-human knockout animal.

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63. The method of Claim 36, wherein said subject is a vertebrate or an invertebrate organism.

64. The method of Claim 36, wherein said subject is a mammal.

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65. The method of Claim 64, wherein said mammal is a human.

66. A method of modulating Wnt-1 and Wnt-3 activity in a subject comprising administering an agent which modulates target Ror2 molecule expression or activity in an amount effective to regulate Wnt-1 and Wnt-3 activity.

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67. A method for identifying an agent for modulating bone-related activity comprising: (a) expressing Ror molecule in a cell or using endogenous Ror expression; (b) contacting the cell with the agent; and (c) monitoring the expression or the activity of Ror molecule wherein an increase or decrease in the expression or activity of Ror molecule in the presence of the agent identifies the agent as modulating bone-related activity.

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68. The method of Claim 67, wherein Ror molecule is Ror1 molecule.

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69. The method of Claim 67, wherein Ror molecule is Ror2 molecule.

70. The method of Claim 67, wherein Ror molecule activity is tyrosine kinase activity.

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71. The method of Claim 67, wherein bone-related activity is osteoblast differentiation, osteoclast differentiation, osteoblast survival, osteoclast survival, osteoblast activity, or osteoclast activity.

72. The method of Claim 67, wherein said agent is selected from the group consisting of antibody, small molecule, peptide, oligopeptide, ribozyme, and polypeptide.
- 5 73. The method of Claim 67, wherein said agent comprises an antisense nucleic acid or siRNA molecule specific for Ror gene and wherein antisense nucleic acid or siRNA molecule recognize and bind to a nucleic acid encoding one or more Ror polypeptides or homologues or derivatives or fragments or variants or mutants thereof.
- 10 74. The method of Claim 73, wherein Ror gene is Ror1 gene and Ror polypeptide is Ror1 polypeptide.
75. The method of Claim 73, wherein Ror gene is Ror2 gene and Ror polypeptide is Ror2 polypeptide.
- 15 76. The method of Claim 67, wherein said agent modulates expression and/or activity of Ror molecules or homologues or derivatives or fragments or variants or mutants thereof by binding to Ror binding partners.
- 20 77. The method of Claims 76, wherein Ror molecule is Ror2 molecule and Ror binding partner is Ror2 binding partner.
78. The method of Claim 77, wherein Ror2 binding partners are selected from the group consisting of ADP/ATP carrier protein, UDP-glucose ceramide
25 glucosyltransferase-like 1, 14-3-3 protein beta/alpha, 14-3-3 protein gamma, ribophorin I, arginine N-methyltransferase 1, cellular apoptosis susceptibility protein, NOTCH2 protein, and human skeletal muscle LIM-protein 3.
79. The method of Claim 67, wherein said agent modulates binding of Ror
30 molecules or homologues or derivatives or fragments or variants or mutants thereof to Ror binding partners.
80. The method of Claims 79, wherein Ror molecule is Ror2 molecule and Ror binding partner is Ror2 binding partner.

81. The method of Claim 67, wherein the cells are primary osteoblasts, immortalized cell lines of osteoblastic origin, or immortalized cell lines of non-osteoblastic origin

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82. The method of Claim 81, wherein immortalized cell lines of osteoblastic origin are selected from the group consisting of HOB, U2OS, and SaOS-2 cells.

83. The method of Claim 67, wherein the agent is further administered to a vertebrate organism to monitor the expression or the activity of Ror molecule wherein an increase or decrease in the expression or activity of Ror molecule in the presence of the agent identifies the agent as modulating bone-related activity.

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84. The method of Claim 83, wherein said vertebrate organism is a mammal.

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85. The method of Claim 83, wherein said vertebrate organism is a non-human transgenic animal.

86. A method for identifying an agent for modulating Wnt signaling pathway comprising: screening one or more agents for the ability to modulate expression or activity of Ror molecule, wherein the agent that can modulate expression or activity of Ror molecule is an agent that modulates Wnt signaling pathway.

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87. A method of linking a bioactive molecule to a cell expressing a Wnt polypeptide, said method comprising contacting a cell with a Ror2 polypeptide that is bound to a bioactive molecule and allowing a Wnt polypeptide and said Ror2 polypeptide to bind to one another, thereby linking said bioactive molecule to said cell.

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88. The method of Claim 87, wherein Wnt polypeptide is selected from the group consisting of Wnt-1 and Wnt-3.

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89. A method for screening a subject for a bone-related disorder comprising the steps of: measuring the expression of Ror molecule in a subject and determining the relative expression of said Ror molecule in the subject compared to its expression in

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normal subjects, or compared to its expression in the same subject after being treated for bone-related disorders.

5 90. A method of identifying genes that participate in bone formation comprising:
a) overexpressing Ror molecule in a cell, b) monitoring the changes in gene
expression profile and c) determining which genes are regulated by Ror expression
thereby identifying genes that participate in bone formation.

10 91. A method of identifying genes that modulate Wnt signaling pathway
comprising: a) overexpressing Ror molecule in a cell, b) monitoring the changes in
gene expression profile and c) determining which genes are regulated by Ror
expression thereby identifying genes that modulate Wnt signaling pathway.

15 92. A method for identifying proliferating human pre-osteoblastic cells using Ror2
as a marker, comprising determining expression of Ror2 gene in a human
osteoblastic cell wherein the increased Ror2 expression identifies the cell as being
proliferating pre-osteoblastic cells.